to pass said acid,

d) dialyzing the dispersion in water while the dispersion is so enclosed, and

e) harvesting free hyaluronic acid from within the semi-permeable membrane.

20. (Amended) A free-acid form of hyaluronic acid suitable for placement permanently or temporarily in the body, made by the method comprising the steps of:

a) preparing a solution of sodium hyaluronate in distilled water,

b) mixing into said solution an acid capable of producing a pH of 2.2 or lower at concentrations in water at 25° C in the range of 0.01 Normal to 1 Normal, to produce a mixture,

c) enclosing said mixture in a dialysis bag having a molecular weight cut-off large enough to pass the acid added in step (b),

d) placing the bag in de-ionized water,

e) periodically replacing the de-ionized water with fresh de-ionized water, until the pH of the de-ionized water exceeds 5.0, and

f) harvesting free hyaluronic acid from within the bag.

REMARKS

Applicant thanks the Examiner for the courtesy extended during a telephone interview on July 7, 1999. The following remarks summarize what was discussed during the interview.

First, during the interview, the undersigned explained that, in the interest of simplifying the issues, Applicants would cancel the claims (Claims 9-19) that do not explicitly recite hyaluronic acid. This means that the patents to Choay and Omiya, cited by the Examiner but not specifi-

cally applied to the claims, are no longer relevant, as they do not involve hyaluronic acid.

Next, during the interview, the undersigned explained that, in the previous Declaration of Ellington M. Beavers under Rule 132, filed together with the present application, it had been shown that not all "hyaluronic acid" is alike, and that the method of making the product greatly affects its properties. The undersigned further explained that the term "hyaluronic acid" has been used imprecisely in the field, to the extent that one cannot really accept, at face value, an unsupported assertion, in a reference, that it uses "hyaluronic acid". Finally, the undersigned explained why the two remaining references of record cannot be deemed to disclose or suggest what is claimed here. The above arguments are explained in more detail below.

1. The Previous Declaration of Ellington M. Beavers Shows that Not All "Hyaluronic Acid" is Alike

In his previous Declaration, filed together with the present application, Dr. Beavers presented the results of several experiments, showing that the method used to make hyaluronic acid significantly affects the properties of the resulting product. Specifically, Dr. Beavers showed that when one follows the directions contained in one of the prior art references (cited in the parent application) for making hyaluronic acid, the result is a product which is not suitable for implantation within the body. The latter product is both cytotoxic (harmful to tissues), and hemolytic (tending to destroy blood cells), and therefore could not be used in the medical applications contemplated by the present invention.

The product claimed in the present application, however, does not suffer from the above disadvantages. The product of the present invention is

suitable for placement permanently or temporarily in the body.

Thus, not all "hyaluronic acid" is alike; in particular, not all hyaluronic acid is of medical grade. The claims of the present application have been amended to require that the product be of medical grade, i.e. that it be suitable for placement in the body. Thus, the claims now specify a critical property of the material produced by the disclosed process.

Applicants submit that, unless a reference indicates that it uses or produces hyaluronic acid of medical grade, one cannot assume that it does so, and one therefore cannot use that reference to reject the present claims.

In short, Applicants submit that the original Declaration of Ellington M. Beavers shows that it matters <u>how</u> the hyaluronic acid is made, and that what is claimed here is <u>not</u> what was known or disclosed in the prior art.

2. The Industry Has Used the Term "Hyaluronic Acid" in a Confusing and Misleading Manner; Unsupported Use of the Term in a Reference Cannot Be Interpreted to Mean the Free Acid

The term "hyaluronic acid" has been widely misused in the industry and in the academic literature. Typically, the term "hyaluronic acid" is used when what is really meant is the sodium salt (sodium hyaluronate). This confusion is explained by the Second Declaration of Ellington M. Beavers, attached to this Amendment.

In his Second Declaration, to which there are attached two articles, Dr. Beavers describes the widespread misuse of the term "hyaluronic acid". A clear example of such misuse occurs in the article from <u>Journal of Histochemistry and Cytochemistry</u>, in which the author describes various "batches" of salts of mucopolysaccharides. Although the salts of other mucopolysaccharides are correctly described, the reference refers to sodium

hyaluronate as "hyaluronic acid". In effect, the author of the article was using the term "hyaluronic acid" to refer to the polymer generically. This imprecise language is typical of the practice in the field.

This confusion prompted another author (see Exhibit B to the Declaration of Dr. Beavers) to propose that the term "hyaluronan" be used to identify the polymer generically, thereby reserving the terms "hyaluronic acid" and "sodium hyaluronate" to designate the free acid and the sodium salt, respectively. The latter proposal has not been universally adopted, and much confusion of terminology persists.

This confusion is demonstrated most dramatically in Paragraph 7 of the Declaration of Dr. Beavers. This paragraph describes the efforts of Dr. Beavers and his colleagues to purchase samples of free hyaluronic acid, both before and after the making of the present invention. Most of the primary chemical suppliers indicated that they could supply only the sodium salt, not the free acid. In one case, a supplier appeared to advertise the free acid, but upon further inquiry, the supplier was obliged to admit that it was selling only the sodium salt. In another case, a supplier claimed it could provide the free acid, but after testing of the product by Applicants, it was determined that the supplier was selling only the sodium salt.

The experience of Dr. Beavers suggests that free hyaluronic acid is <u>not</u> commercially available, and that those persons who advertise it for sale invariably do not have the free acid, but are really selling the sodium salt. This conclusion is undoubtedly due, in part, to the confusion in terminology, discussed above. Due to this confusion, suppliers tend to refer to "hyaluronic acid" generically, when what is really meant is the sodium salt.

3. The References Do Not Disclose or Suggest the Present Invention

Of the four references cited by the Examiner, only two (Schultz and de Belder) mention hyaluronic acid. Applicants submit that neither reference anticipates or suggests the present invention.

Although the patent to Schultz purports to cover both hyaluronic acid and its sodium salt, the patent freely admits (column 4, line 61 through column 5, line 6) that all of the data described in the patent were obtained with the sodium salt only, and not with the free acid. Indeed, the patent proposes to use the term "hyaluronic acid" generically, to include the sodium salt. In so doing, the Schultz patent adopts the confusing and misleading terminology that has caused so many problems, as described above.

Because Schultz admits that all of its data pertain to the sodium salt and not the free acid, the only disclosure of free acid is imaginary. It is therefore impossible to know whether the free hyaluronic acid imagined by Schultz would have been of medical grade, as required by the pending claims. There is simply insufficient disclosure, in Schultz, to support the existence of a hyaluronic acid of medical grade. For this reason, Applicants submit that Schultz cannot be deemed to anticipate or suggest the claimed product.

The patent to de Belder contains various examples showing the use of sodium hyaluronate, the salt which is so commonly called "hyaluronic acid". However, at one point, de Belder does claim to use the free acid form (column 4, lines 43-52). But, as is explained in the Declaration of Dr. Beavers, the material is reacted in the presence of glacial acetic acid.

Dr. Beavers' Declaration explains that the glacial acetic acid would be necessary only if the material is the salt, not the free acid. The free acid form would have a pH in the range claimed by de Belder (i.e. 2-5), and there would be no need to provide glacial acetic acid.

The inescapable conclusion is that de Belder did not really try hyaluronic acid, in the free acid form. Quite possibly, de Belder used a substance which had been advertised as the free acid form, but which really was not. Errors of this kind are particularly likely, in view of the experience of Dr. Beavers, set forth in his Declaration.

In any event, Applicants note further that de Belder says nothing about how the alleged free hyaluronic acid was made. Therefore, from the information in the patent, one cannot know whether the "hyaluronic acid" envisioned by de Belder was of medical grade, as required by the present claims. For this additional reason, Applicants submit that de Belder does not teach or suggest a hyaluronic acid of medical grade, and that the present claims therefore define a patentable invention.

In summary, Applicants have shown that the method of manufacture of hyaluronic acid critically affects the properties of the resulting product. Applicants have also shown that the term "hyaluronic acid" has been used loosely, and confusingly, in the field, and that what is represented commercially as "hyaluronic acid" is invariably the salt thereof. Finally, Applicants have shown that the references which mention the free acid, fail to provide any proof that real hyaluronic acid was used. Moreover, such references fail to disclose a hyaluronic acid which is of medical grade, which is what is now specifically claimed.

For the reasons given above, Applicants submit that the application, as amended, is in condition for allowance. Applicants request reconsideration, and early favorable action, by the Examiner. If the Examiner has questions, Applicants request that he telephone the undersigned to expedite the prosecution of this case.

Respectfully submitted,

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